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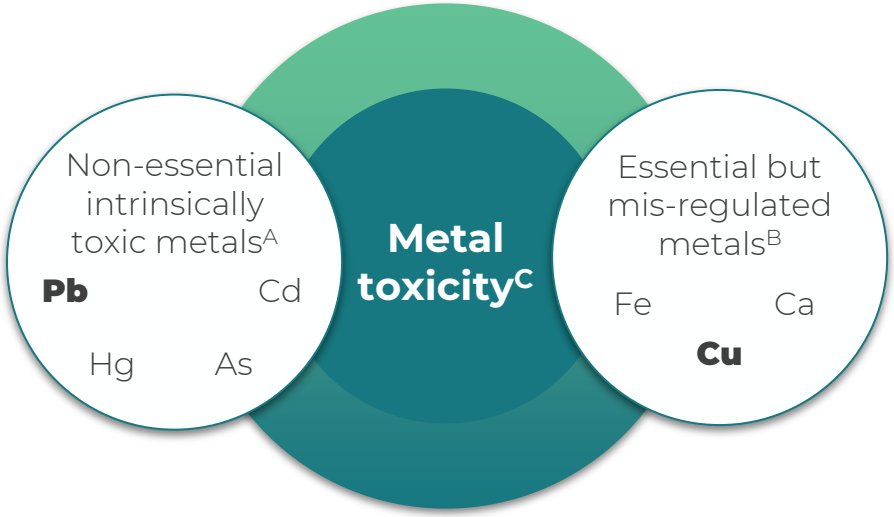
# metaLead

**treating metal-related diseases.**
**effectively.**

VENTURE KICK · BASELAUNCH · UZH Entrepreneur Fellowships · BII BioInnovation Institute · Innosuisse · >>venture>> WINNER · SNF · TDA Therapy Development Accelerator · University of Zurich[UZH]

# **Metal-related diseases** impact many globally

**Two types of toxic metals can accumulate, negatively affecting human health**

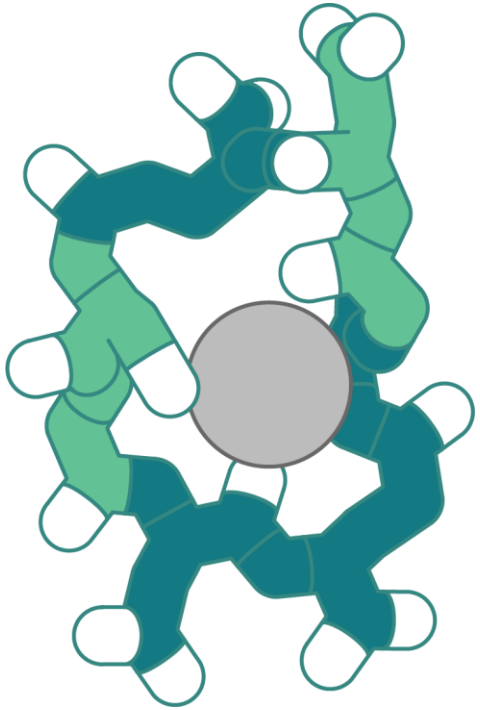



| Disease area | Prevalence | Global population | US annual market size |
|---|---|---|---|
| Cu - Wilson's Disease | 1 in 30,000 globally[D] | 267k | **$0.5 B[H]** |
| Pb - Lead Poisoning | 1 in 3 children globally[E] | 800 million[E] | **$0.2 B[I]** |
| Cu - Menkes Disease | 1 in 35,000 male births[F] | 10k[L] | **$0.3 B[J]** |
| Fe - NBIA | 1-3 per 1,000,000 globally[G] | 15-20k[G] | **$0.3 B[K]** |

A. WHO (2020), 10 chemicals of public health concern; B. Bleakley & MacGIllivray (2011) Transition metal homeostasis: from yeast to human disease; C. Shoshan, M. (2022) Will Short Peptides Revolutionize Chelation Therapy? Chimia 76, p. 744-747; D. Roberts & Schilsky (2023). Current and Emerging Issues in Wilson's Disease; E. Unicef (2020) The toxic truth. F; https://www.nationwidechildrens.org/conditions/menkes-disease G. NBIAdisorders.org; H. 66% insured, price of $221,000, 30% mkt share; I. BLL 20-45, 137k patients * 70% mkt share, BLL > 45 130k patients * 40% mkt share J. 3.8 m US births, 51% male, 550 patients in 10 yrs, $500,000 for treatment ; K. $400,000 for treatment; L. Over 10 years

# metaLead develops **best-in-class chelating agents**

**Highly effective, tailored to capture**
excellent metal selectivity and affinity



**Benign**
do not interact with essential metals
do not hijack ions from metalloproteins
become inert after metal binding

**Stable & orally-available**
as heavily modified

Exclusive license to all **cyclic tetrapeptides** and **metal complexes** thereof for health and environmental remediation applications.
**WO2022117877** | **PCT-EP4008714**, ongoing national phase, **FTO** in place.

# Wilson's is a **lifelong rare genetic disease**



## A lifelong genetic disease

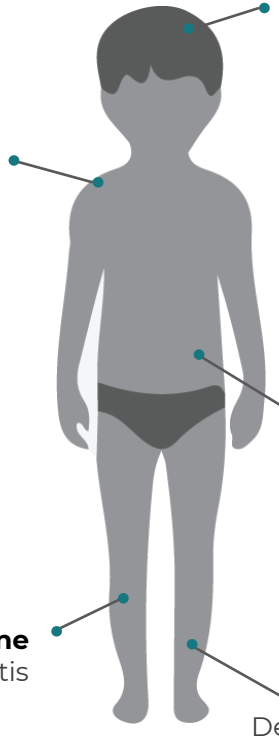
**Toxic accumulation of Cu**
in the liver and blood
(mutated
ATP7B gene)

Onset between **5-35 years**

**Requires immediate lifelong chronic treatment**

Treatment delays may cause **irreversible** damage

## Multiple presentations



**Brain**
Persistent neurological issues: tremors, involuntary muscle movements, clumsy gait and speech difficulties
Psychological issues, e.g. depression, bipolar, psychosis, personality changes

**Liver**
Mild liver disease
Fatty Liver
Cirrhosis
Liver failure (5-10% of cases)

**Kidney**
Kidney damage

**Bone**
Arthritis

Destruction of red blood cells leading to anemia and jaundice

## **1 in 30,000** live with Wilson's disease



**11,000+**
in the US

**24,000+**
in Europe

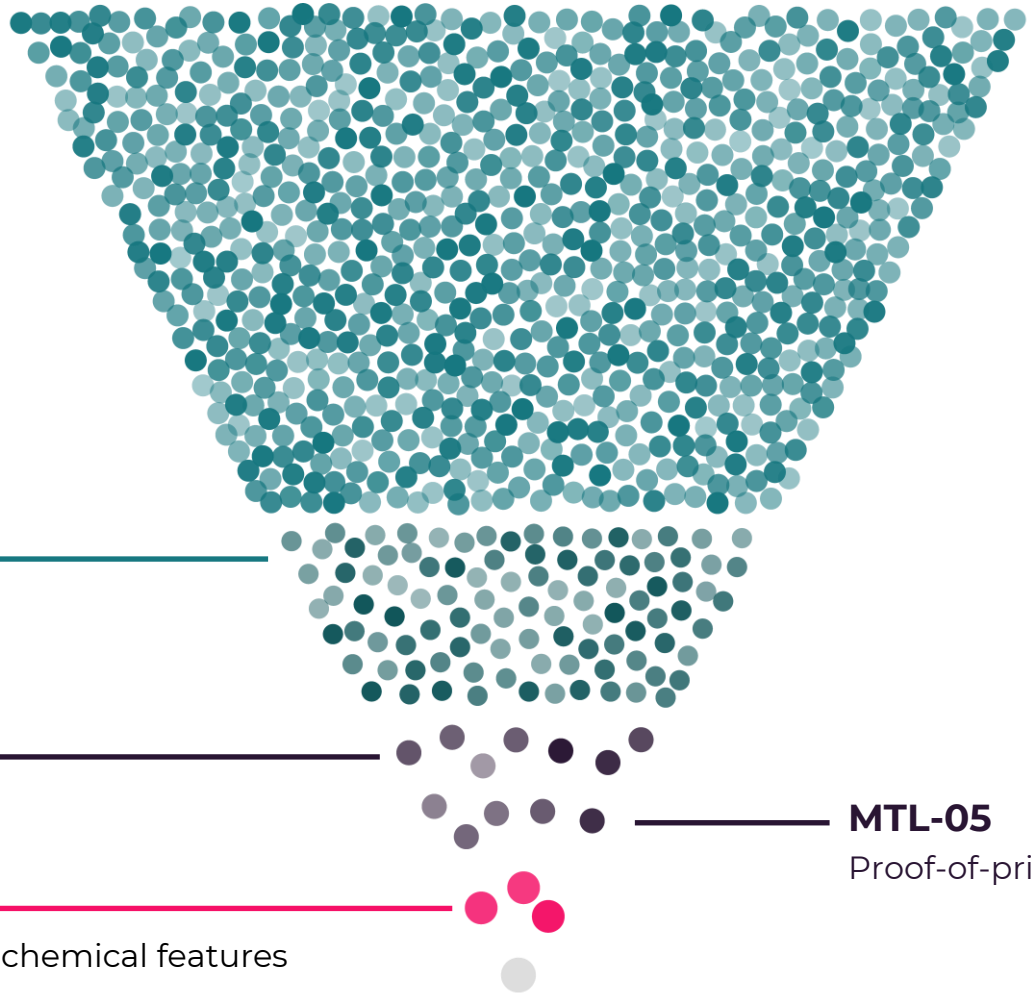
**47,000+**
in China

https://www.mayoclinic.org/diseases-conditions/wilsons-disease/symptoms-causes/syc-20353251; WD review

Wilson's disease

# **12 hits** identified through *in silico* evaluation

**8100 theoretical peptides**
>70k analyzed structures
Same scaffold; covered by current IP
Expected to bind Cu(II) ions
Straightforward CMC



**110 fulfilled requirements**
Cu(II) binding affinity: Logβ
between 15-22

**12 hits**
Zn(II) binding affinity: As low as possible

**3 candidates**
*In vitro* efficacy and safety, excellent physico-chemical features

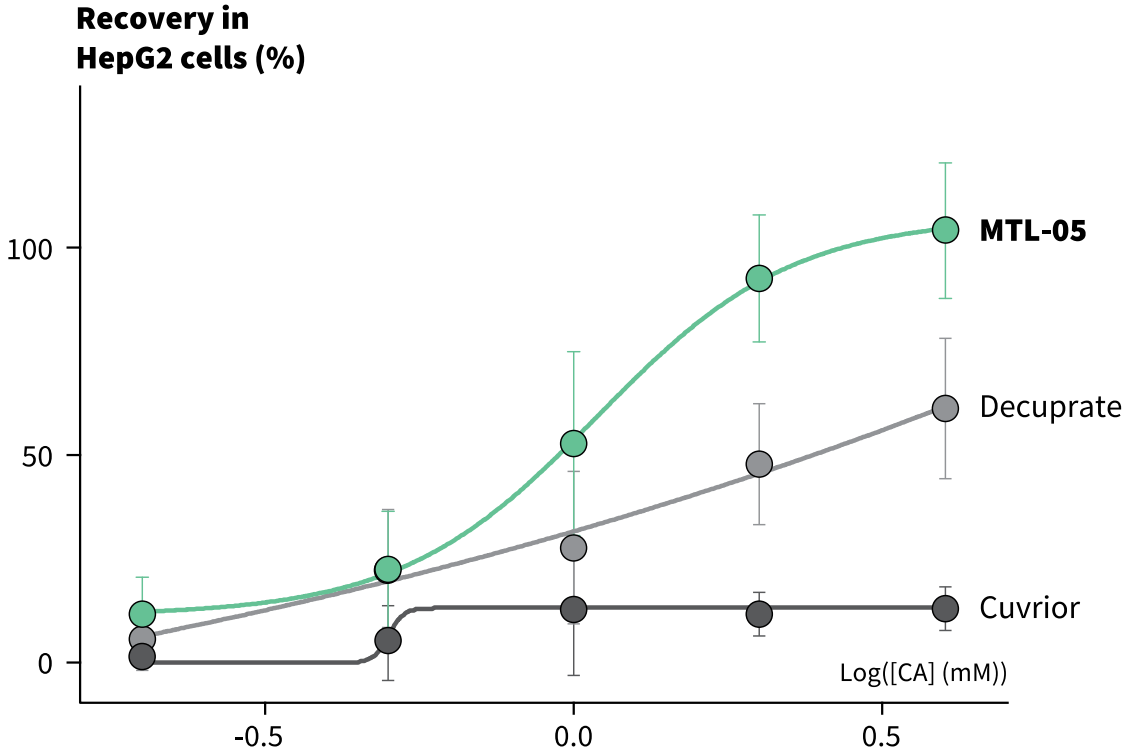
**MTL-05**
Proof-of-principle *in vitro* candidate

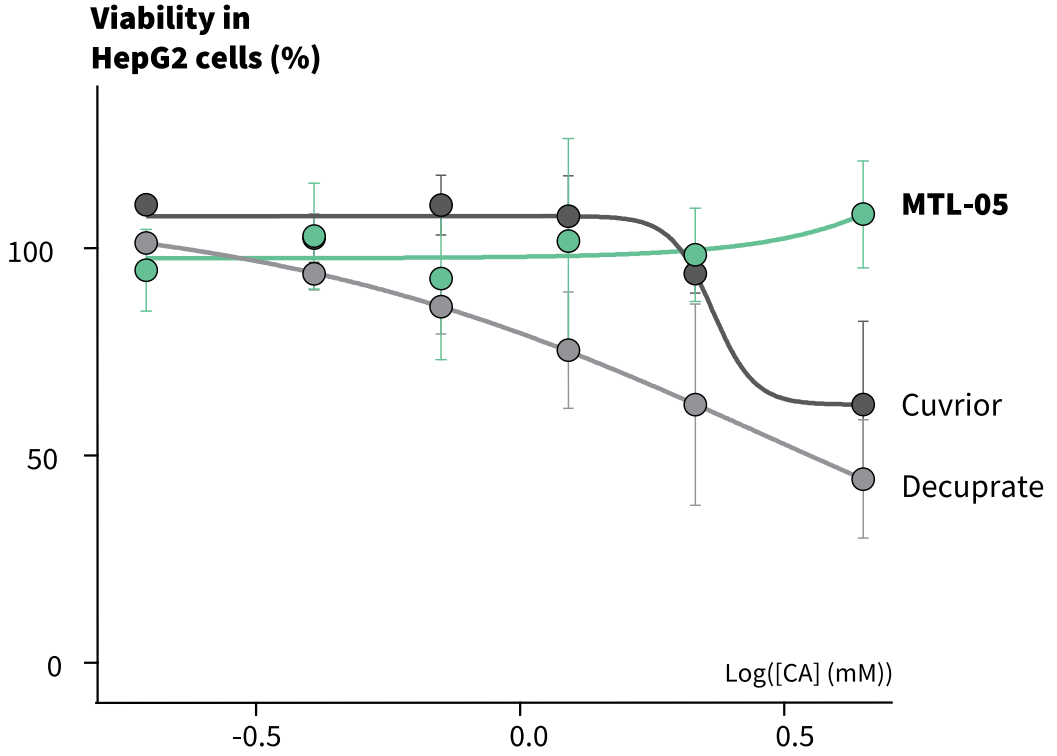
**MTL-X**
lead candidate
Validated *in vivo*

DFT-D3 & COSMO-RT $\Delta G_{comp}$ with Cu(II) and Zn(II);
In collaboration with Prof. Lubomír Rulíšek, IOCB Prague

# MTL-05 **recovers 100%** of copper-exposed cells

Wilson's disease



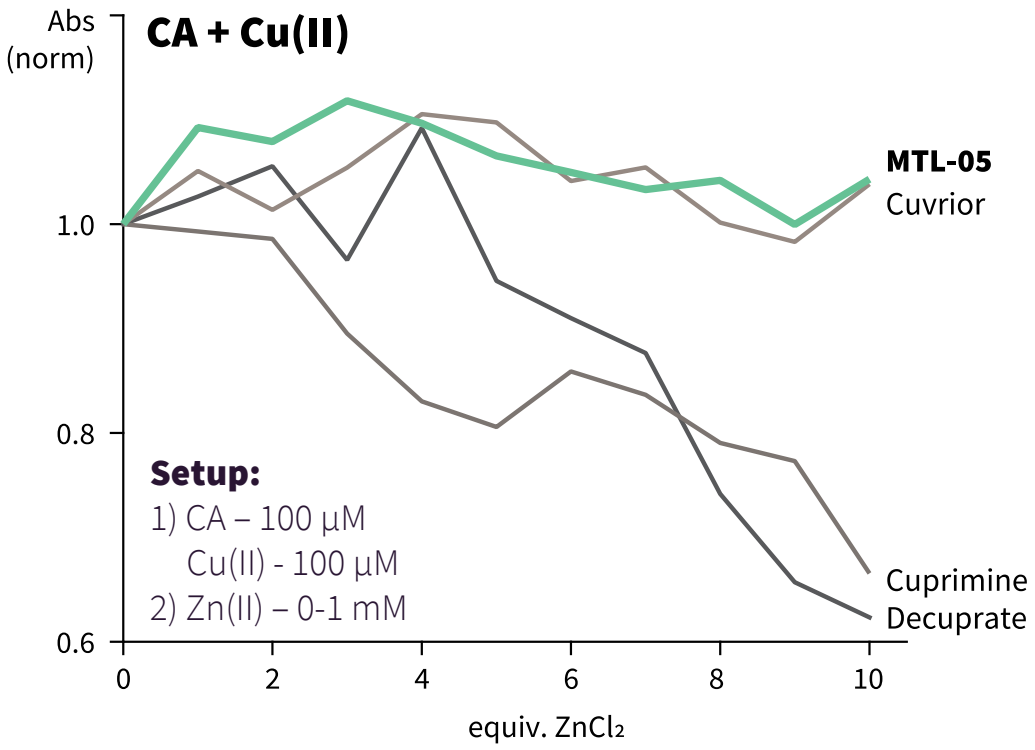

MTL-05 **fully recovers Cu-exposed human cells**, outcompeting both Cuvrior and Decuprate.

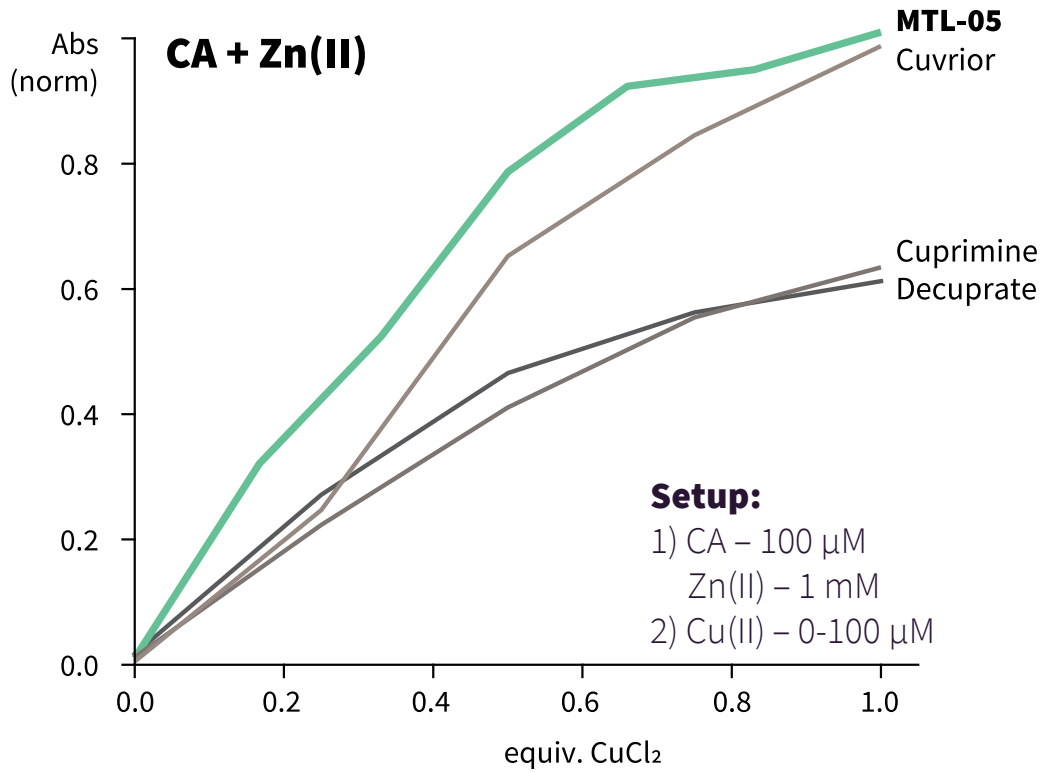
Unlike other chelating agents, MTL-05 **is not cytotoxic**.

CA: chelating agent

# MTL-05 is **stable and selective**

Wilson's disease

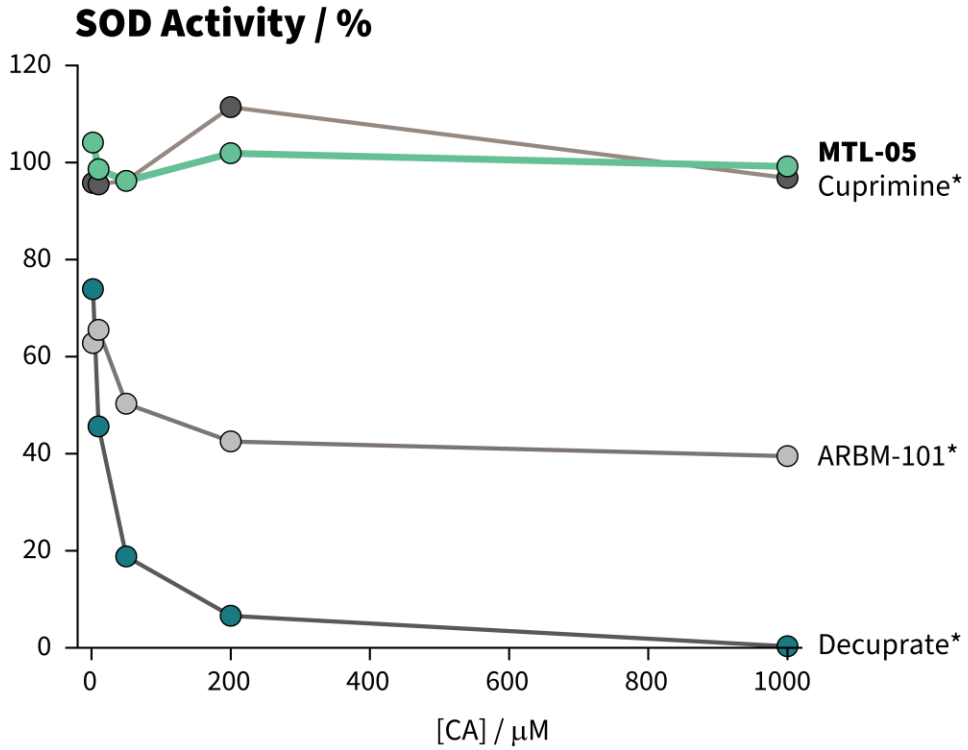


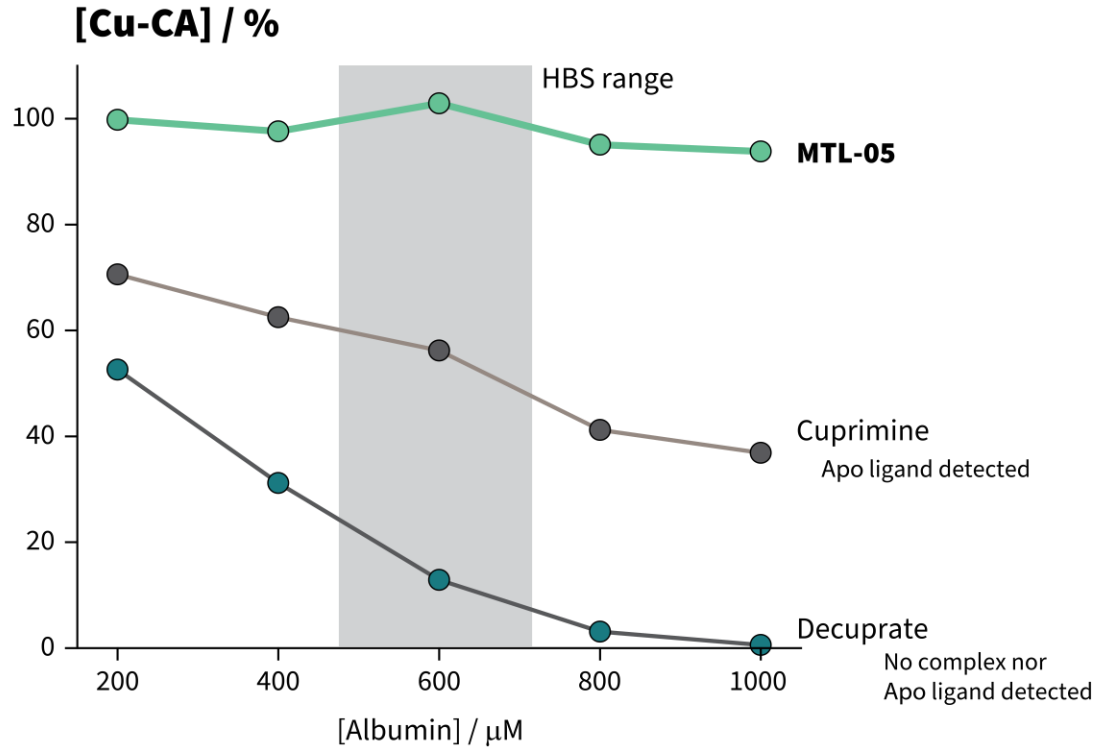




Up to 10 equivalents of $Zn^{2+}$ do not affect the MTL-05 complex.
The complexes with the SOCs, however, are unstable under similar conditions.

CA: chelating agent

# MTL-05 does not interact with **key proteins**

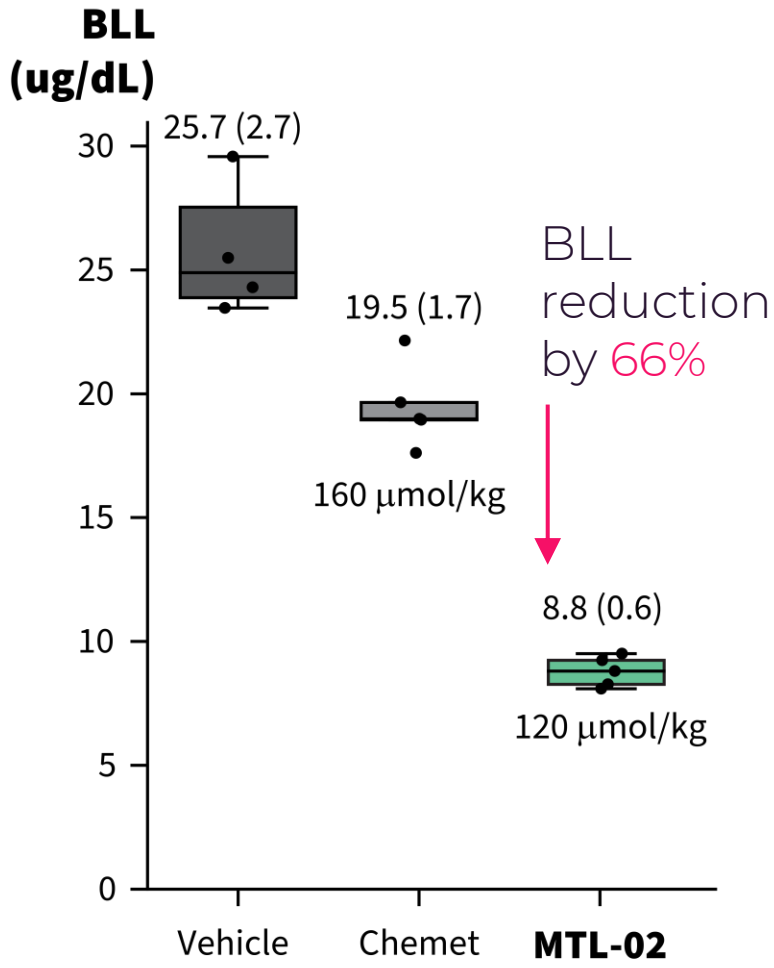


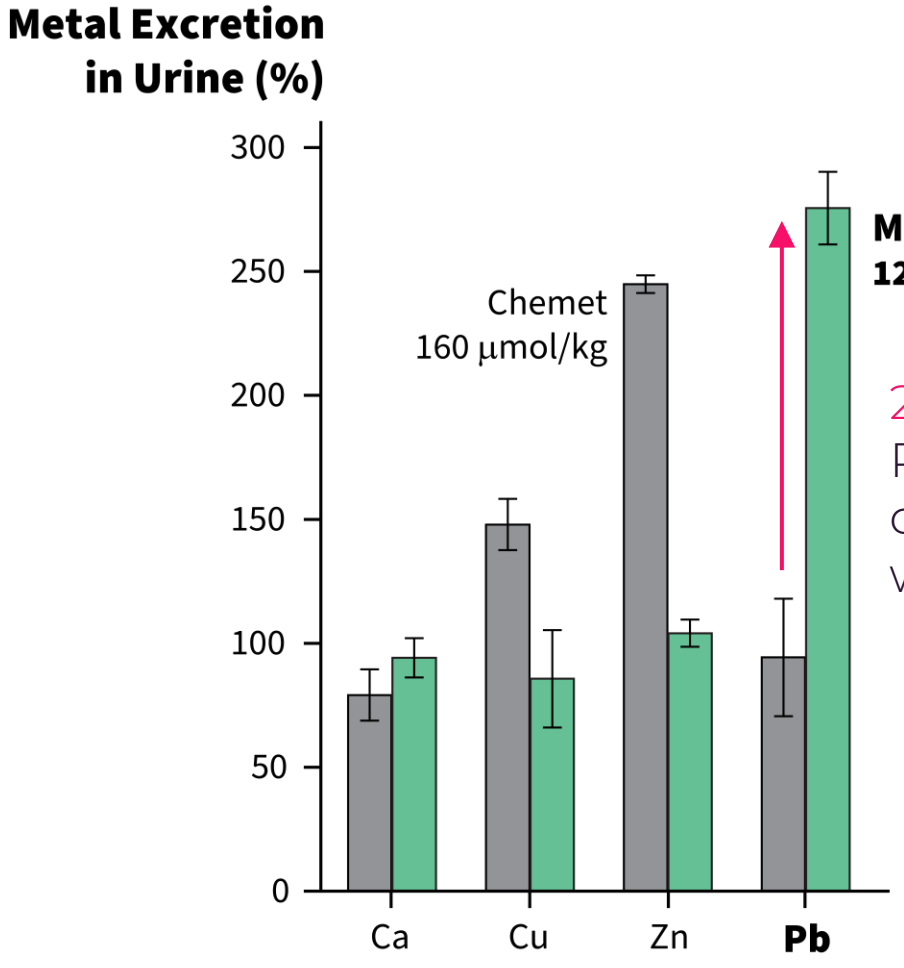

MTL-05 does not inhibit SOD and does not interact with albumin.
Furthermore, albumin does not compete with MTL-05 on Cu(II) binding.

*Gastroenterology 2023, 165, 187–200.
CA: chelating agent
SOD: superoxide dismutase; ubiquitous Cu-containing enzyme responsible for reducing oxidative stress intra- and extracellularly.

# **Efficacy in mice** validated for MTL-02 with Pb



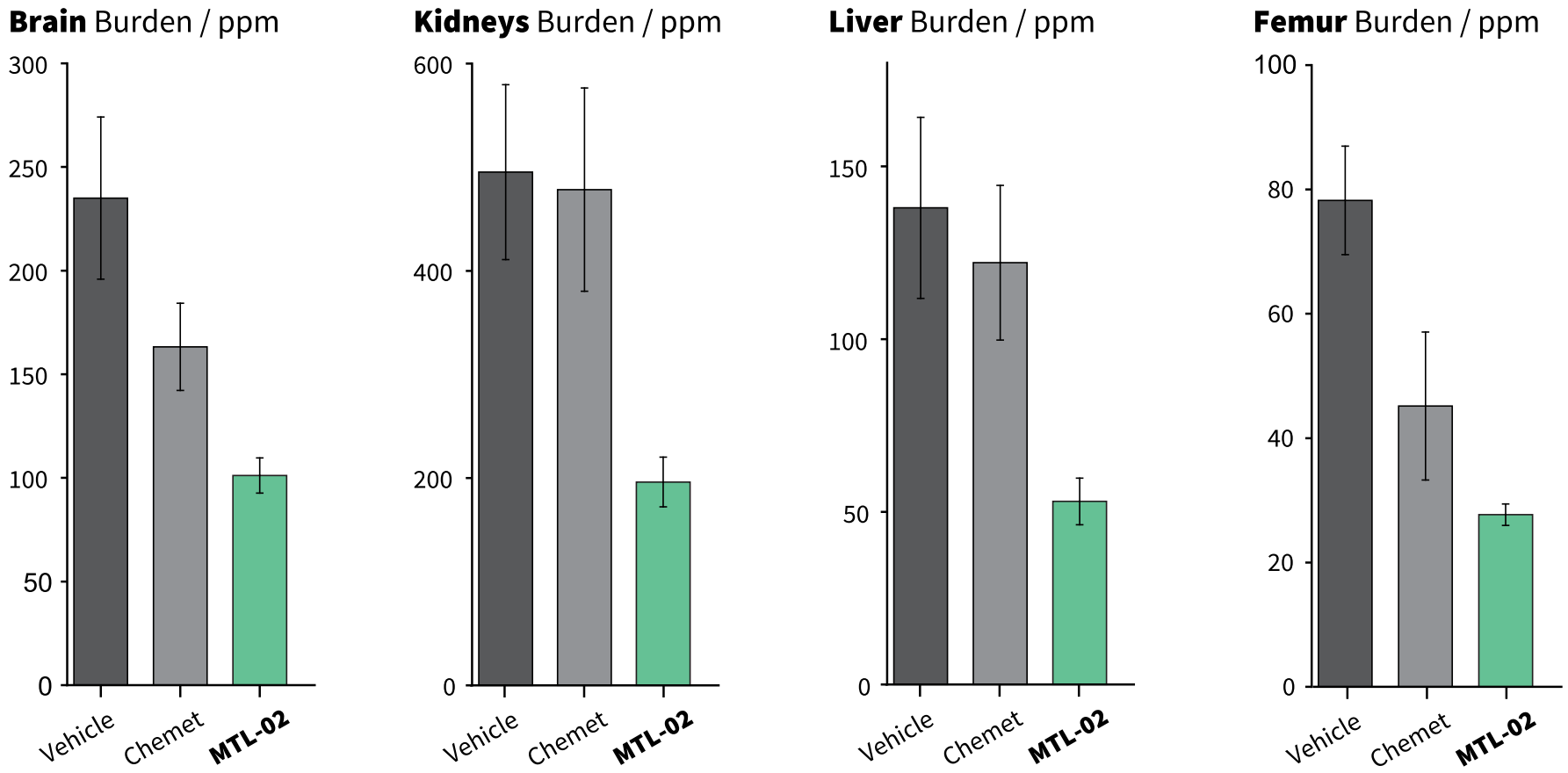

BLL reduction by 66%




200% more Pb removal compared with Chemet

7 days Pb exposure in drinking water; 15 days treatment (single daily dose); 5 mice per group; Samples 7 days after the last dose
BLL: Blood lead level

# MTL-02 **decreases Pb burden**




Organ burden reduced by 57-65% compared with the vehicle and by 38-59% compared with Chemet, but with a lower dose.

# **Chelation therapy** is the dominant modality

Wilson's disease

## Chelation Therapy

is the dominant standard of care

BAUSCH Health  Orphalan

- ✓ Effective for <70% of patients
- ✓ Oral treatment
- ✗ Lifelong treatment
  Low adherence: 2-4 doses daily, requires refrigeration
- ✗ Low selectivity, interacts with other processes, can expel essential metals or re-distribute toxic metals
- ✗ Many side effects *e.g.,* gastrointestinal, nausea, neurological

## Gene therapy

is emerging into the landscape

ultragenyx  Vivet THERAPEUTICS

- ✓ Single treatment, with potential to cure
- ✗ Only 20% eligible for gene therapy (AAV)
- ✗ Likely does not replace the need for chelation
- ✗ Expensive

Additional emerging treatments: Dialysis additive (MexBrain)

# Current chelation therapies are **ineffective**

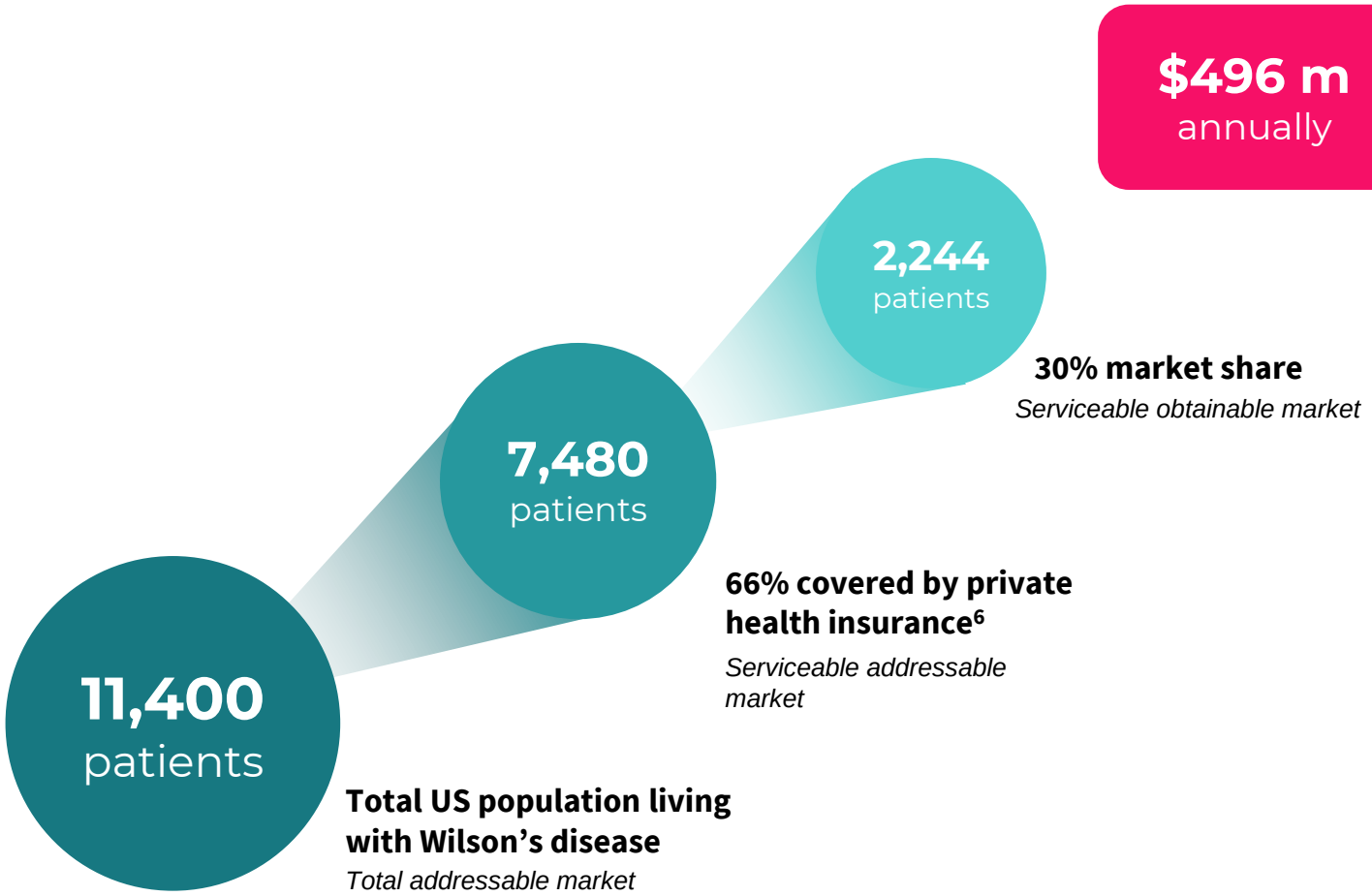
Wilson's disease

| | Market launch | Tech | Efficacy | Selectivity | Safety | Dosage regimen | Storage | Eligible patients |
|---|---|---|---|---|---|---|---|---|
| **Cuprimine (D-pen)** | 1956 | Small molecule | Limited; low Cu affinity | No; interacts with Zn | Interacts with thiolates | Oral 4x daily | 4 °C | <50% symptomatic |
| **Syprine (TRTN)** | 1970 | Small molecule | Sufficient; low Cu affinity | No; interacts with Ca | Interacts with DNA | Oral 2-4x daily | 4 °C | <70% symptomatic |
| **Cuvrior (TRTN)** | 2023 | | | | | | RT | |
| **Decuprate (TTM)** | Terminated in April 2023 | Small molecule | Yes | No | Cu not excreted; Unknown deposition | Oral 1x daily | RT | |
| **ARBM-101 (methanobactin)** | Preclinical | Peptide | Yes | Yes; too high affinity | Interacts with Cu enzymes | IV / IP 1x daily | Unstable at RT | >80% |
| **MTL-05** | Preclinical | **Peptide** | **Yes** | **Yes** | **Yes** | **Oral 1x daily** | **RT** | **>80%** |

# $0.5 B market potential annually in the US

Wilson's disease

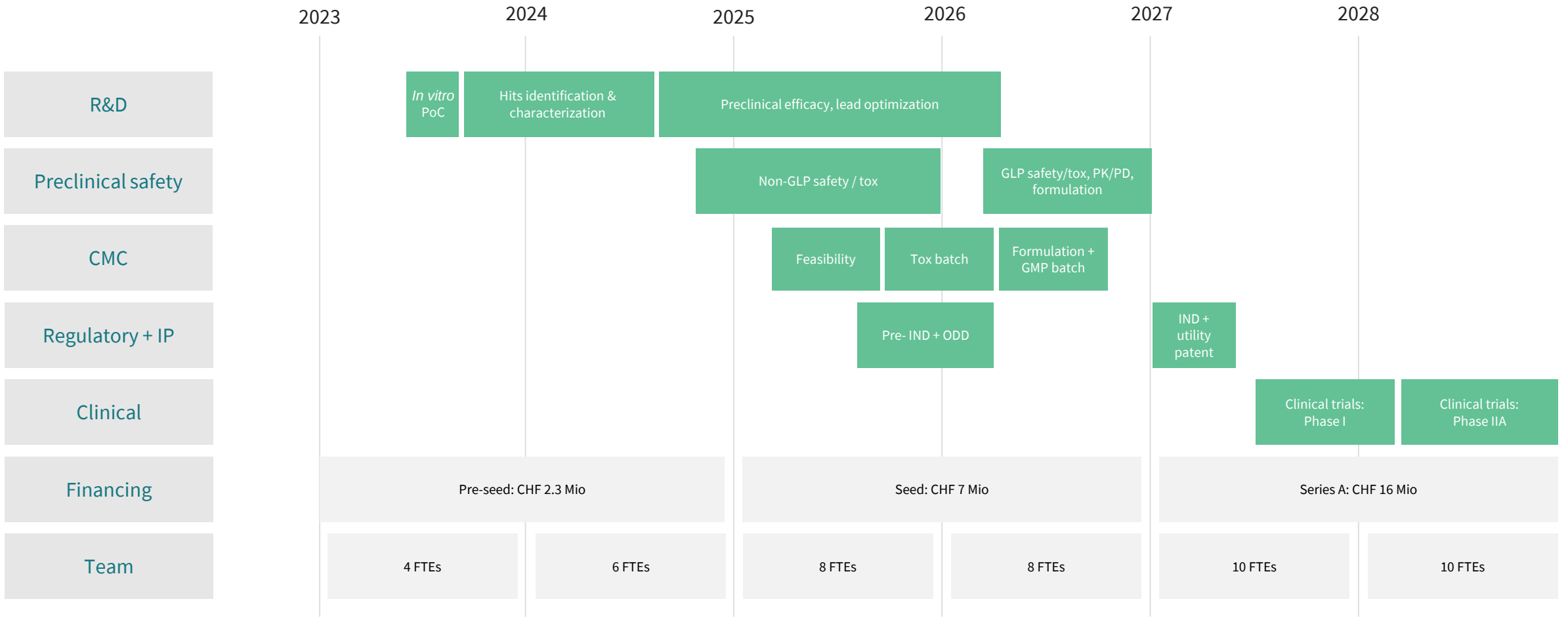
| Medication | Annual prices |
|---|---|
| **Cuprimine (D-pen)** | Generic: $81,322 - $139,445<br>Brand name $402,755.60[1] |
| **Syprine (TRTN)** | Generic: $46,961 - $93,922<br>Brand name: $163,542 - $327,084[2] |
| **Cuvrior (TRTN)** | $147,000 - $294,000[3] |
| **Decuprate (TTM)** | Acquisition price: $855m<br>Phase III program terminated in April 2023, due to low expulsion levels of Cu in the urine[4] |
| **MTL-05** | **$221,000** |




(1) https://www.drugs.com/price-guide/cuprimine (2) https://www.drugs.com/price-guide/syprine; (2) https://www.drugs.com/price-guide/cuvrior
(3) https://www.drugs.com/price-guide/cuvrior; (4) https://www.fiercebiotech.com/biotech/astrazeneca-dumps-855m-near-approval-rare-disease-drug-after-talks-regulators; (5) Health Insurance Coverage in the US 2022, United States Census Bureau

# metaLead is currently in **preclinical stages**

Wilson's disease



# Meet the team!

**Dr. Michal Shoshan**
Founder and CEO, Board Member
Medicinal inorganic chemist
+14 years in metal-related drug dev.

**Dr. Vincent Forster**
Board Member
Pharmacist | Co-founder and CEO
Versantis AG

**Dr. John Cullity, MD**
Board Member
Hematologist | Health Economist | Serial Entrepreneur

**Dr. Stefano Vavassori**
COO
Immunologist | Entrepreneur
Preclinical and clinical drug dev.

**Dr. Luca Sauser**
Scientist
Medicinal inorganic chemist

**Valerie Thevenoz**
Founder's Associate
Business Development

**Dr. Lise-Marie Fueg**
CMC Consultant
CMC & More GmbH

**Prof. Alan Woolf, MD**
Advisor
Director, Pediatric Environmental Health Center, BCH | Professor of Pediatrics, Harvard Medical School

**Prof. Nicholas Newman, MD**
**Advisor of NIH, CDC, AAP**
Advisor
General and community pediatrician | Head of Pb clinic, Cincinnati Children's Hospital

**Dr. Alexander Fleming**
Regulatory Consultant
Founder & Chairman, Kinexum

**Dr. Hanspeter Nick**
Advisor
30 years in Pharma R&D, Novartis
Area of expertise: Fe chelation

**Prof. Morri Markowitz, MD**
Advisor of NIH, CDC
Director Lead Poisoning Prevention and Treatment Program, Children's Hospital of Montefiore

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# Thank You

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